Appendix 2: Warfarin drug interactions

The tables below provide some common warfarin drug interactions for prescription medications (Table 1), as well as herbal / complementary and over-the-counter (OTC) medications (Table 2). These are not exhaustive lists. There are other clinically relevant interactions. In all cases clinicians should perform a drug interaction search using available online databases.

Whenever starting or stopping a medication, particularly antibiotics, the INR must be re-checked 48 to 72 hours after the change in therapy. Do not pre-empt a change. Make dose adjustments only after checking INR at 48 to 72 hours.

Definitions for Severity of Interaction and Level of Evidence

Severity of Interaction	
Major	The interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects, or the drugs are contraindicated for current use.
Moderate	The interaction may result in an exacerbation of the patient's condition and/or require an alteration in therapy.

Level of Evidence	
A	Controlled studies have clearly established the existence of the interaction.
B	Documentation strongly suggests the interaction exists, but well-controlled studies are lacking.
C	Available documentation is poor, but pharmacologic considerations lead clinicians to suspect the interaction exists; or documentation is good for a pharmacologically similar drug.

Source: (IBM Micromedex, 2022)

Table 1: Warfarin drug interactions with prescription medications

Interacting medication	Risk of bleeding	Proposed mechanism	Severity (Evidence)
Allopurinol	**Increased**	Inhibition of warfarin metabolism	**Major** (B)
Amiodarone	**Increased**	Inhibition of warfarin metabolism	**Major** (A)
Aprepitant	Decreased	Induction of warfarin metabolism	Moderate (A)
Antiplatelet agents (e.g. aspirin)	**Increased**	Additive bleeding risk. Review the need for combination therapy. No effect on INR	**Major** (A)
Azathioprine	Decreased	Unexplained mechanisms	Moderate (B)
Azole antifungals (e.g. fluconazole, miconazole, posaconazole, voriconazole)	**Increased**	Inhibition of warfarin metabolism	**Major** (A, B)

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Interacting medication	Risk of bleeding	Proposed mechanism	Severity (Evidence)
Barbiturates (e.g. phenobarbital, primidone)	Decreased	Induction of warfarin metabolism	Moderate (A)
Bosentan	Decreased	Induction of warfarin metabolism	Moderate (B)
Cannabidiol	**Increased**	Inhibition of warfarin metabolism	**Major** (B)
Capecitabine	**Increased**	Inhibition of warfarin metabolism	**Major** (A)
Carbamazepine	Decreased	Induction of warfarin metabolism	Moderate (B)
Carboplatin	**Increased**	Unexplained mechanisms	**Major** (B)
Cephalosporins	**Increased**	Decreased synthesis of clotting factors	**Major** (B)
Colestyramine	Decreased	Reduced absorption of warfarin	Moderate (B)
Cyclophosphamide	**Increased**	Unexplained mechanisms	**Major** (B)
Cyclosporin	Decreased	Unexplained mechanisms	Moderate (B)
Direct oral anticoagulants (i.e. apixaban, dabigatran, rivaroxaban)	**Increased**	Additive bleeding risk. Review anticoagulant therapy as this combination is contraindicated.	**Major** (B)
Disulfiram	Increased	Inhibition of warfarin metabolism	Moderate (B)
Doxorubicin	**Increased**	Unexplained mechanisms	**Major** (B)
Entacapone	**Increased**	Inhibition of warfarin metabolism	**Major** (B)
Etoposide	**Increased**	Unexplained mechanisms	**Major** (B)
Fibrates (e.g. fenofibrate, gemfibrozil)	**Increased**	Unexplained mechanisms	**Major** (B)
Fluorouracil	**Increased**	Inhibition of warfarin metabolism	**Major** (A)
Gemcitabine	**Increased**	Unexplained mechanisms	**Major** (B)
Griseofulvin	Decreased	Induction of warfarin metabolism	Moderate (B)
Imatinib	**Increased**	Inhibition of warfarin metabolism	**Major** (B)

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Interacting medication	Risk of bleeding	Proposed mechanism	Severity (Evidence)
Isoniazid	Increased	Unexplained mechanisms	Moderate (B)
Leflunomide	**Increased**	Inhibition of warfarin metabolism	**Major** (B)
Macrolide antibacterials (e.g. azithromycin, erythromycin, clarithromycin)	**Increased**	Inhibition of warfarin metabolism	**Major** (A)
Mercaptopurine	**Decreased**	Unexplained mechanisms	**Major** (B)
Methotrexate	**Increased**	Unexplained mechanisms	**Major** (B)
Metronidazole	**Increased**	Inhibition of warfarin metabolism	**Major** (B)
Mirtazapine	**Increased**	Unexplained mechanisms	**Major** (A)
Non-steroidal anti-inflammatory drugs (NSAIDs)	**Increased**	Additive effect on haemostasis No effect on INR	**Major** (C)
Oseltamivir	**Increased**	Unexplained mechanisms	**Major** (B)
Paracetamol	Increased	Inhibition of warfarin metabolism	Moderate (A)
Penicillins – dicloxacillin and flucloxacillin	**Decreased**	Induction of warfarin metabolism	**Major** (A)
Penicillins – benzylpenicillin, phenoxymethylpenicillin and ticarcillin	**Increased**	Inhibition of warfarin metabolism	**Major** (B)
Phenytoin	Initially increased. Decreased with long-term use	Inhibition or induction of warfarin metabolism	Moderate (C)
Propylthiouracil	Decreased	Reduced catabolism of clotting factors	Moderate (B)
Proton pump inhibitors (e.g. omeprazole, pantoprazole)	Increased	Inhibition of warfarin metabolism	Moderate (B)
Quetiapine	Increased	Unexplained mechanisms	Moderate (B)
Quinolone antibacterials (e.g ciprofloxacin, moxifloxacin, norfloxacin)	**Increased**	Inhibition of warfarin metabolism; disruption of vitamin K synthesis	**Major** (A)
Rifamycins (e.g. rifabutin, rifampicin)	Decreased	Induction of warfarin metabolism	Moderate (B)

Continued overleaf

Interacting medication	Risk of bleeding	Proposed mechanism	Severity (Evidence)
Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. citalopram, fluoxetine, fluvoxamine, sertraline)	**Increased**	Unexplained mechanisms	**Major** (B)
Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) (e.g. desvenlafaxine, venlafaxine)	**Increased**	Unexplained mechanisms	**Major** (B)
Statins (e.g. fluvastatin, simvastatin, rosuvastatin)	**Increased**	Inhibition of warfarin metabolism	Moderate – **Major** (A, B)
Sulfa antibacterials (e.g. sulfamethoxazole included in Co-trimoxazole)	**Increased**	Inhibition of warfarin metabolism	**Major** (A)
Tamoxifen	Increased	Inhibition of warfarin metabolism	Contraindicated (B)
Testosterone	**Increased**	Modification of coagulation factor, hepatic synthesis, and competitive inhibition of plasma protein binding	**Major** (B)
Tramadol	Increased	Unexplained mechanisms	Moderate (B)
Valproate	**Increased**	Displacement of warfarin from protein-binding sites and inhibition of warfarin metabolism	**Major** (B)
Vancomycin	Increased	Unexplained mechanisms	Moderate (B)

Source: (IBM Micromedex, 2022), (UW Medicine Pharmacy Services, 2022)

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Table 2: Warfarin drug interactions with complementary medications

Interacting complementary medication	Risk of bleeding	Proposed mechanism	Severity (Evidence)
Co-enzyme Q10	Decreased	Similar chemical structure to vitamin K	Moderate (B)
Dan shen / Tan shen (*Salvia miltiorrhiza*)	**Increased**	Increased serum concentration and bioavailability of warfarin	**Major** (B)
Fish oil	**Increased**	Decreased platelet aggregation due to inhibition of thromboxane	**Major** (B)
Garlic supplement	**Increased**	Additive anticoagulant effect; Increased fibrinolytic activity; Possible inhibition of platelet aggregation	**Major** (B)
Ginger supplement	Increased	Additive antiplatelet effect; Possible inhibition of thromboxane formation	Moderate (B)
Gingko supplement	**Increased**	Increased risk of bleeding due to Inhibition of platelet aggregation No effect on INR	**Major** (B)
Glucosamine +/- chondroitin	Increased	Unexplained mechanisms	Moderate (B)
Milk thistle (*Silybum marianum*)	Increased	Additive anticoagulant and antiplatelet effect	Unknown (C)
St John's Wort	**Decreased**	Induction of warfarin metabolism	**Major** (B)
Vitamin E	Increased	Decreased synthesis of clotting factors	Moderate (B)

Source: (IBM Micromedex, 2022) (Bijak & Saluk-Bijak, 2017)

References

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